CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-612

ADMINISTRATIVE DOCUMENTS

MEMO

RE: Lidoderm™ Patch Labeling
FROM: Dan Wang, Ph.D. 3/18/99
TO: Victoria Lutwak
THROUGH: Dennis Bashaw, Pharm.D. 11/25/98
DATE: Nov. 24, 1998

The pharmacokinetics section of the latest labeling for Lidoderm™ Patch has been reviewed and found acceptable. The sponsor has revised the labeling according to the Agency's comments.

EXCLUSIVITY SUMMARY for NDA # 20-612 **SUPPL #** _____

Trade Name Lidoderm **Generic Name** Lidocaine Patch

Applicant Name Hind Health Care **HFD-** 550

Approval Date, if known March 19, 1999

PART I **IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /___/ NO /✓/

If yes, NDA #_____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 8816 2% Lidocaine

NDA# 9407 2% Lidocaine

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

YES /___/ NO /✓/

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

#1 Study 654-D-323 Cross session study of topical Lidocaine patches

#2 Study CX2A 2005 Crossover withdrawal study

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

See previous page _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

NOTE: This product has received orphan designation.

/S/ _____ March 19, 1999

Signature Date

Title: Project Manager

/S/ 3-19-99

Signature of Division Director Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-612 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-550 Trade (generic) name/dosage form: Lidoderm (lidocaine Patch) Patch 5% Action: AP AE NA

Applicant Hind Health Care Therapeutic Class 3S

Indication(s) previously approved Management of Pain - Topical 2% cream

Pediatric labeling of approved indication(s) is adequate ___ inadequate ✓

Indication in this application Post-Herpetic Neuralgia

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ ___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

/S/

Signature of Preparer and Title (PM, CSO, MO, other)

March 18, 1999

Date

cc: Orig NDA/PLA # 20-612
HFD 550 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

May 30, 1996

LIDOCAINE PATCH NDA 20-612

In accordance with 21 U.S.C. § 306 of the Federal Food, Drug and Cosmetic Act, this is to certifiy that no person, who has been or will be employed in connection with the development of Lidocaine Patch for post-herpetic neuralgia (IND , NDA 20-612), shall be disbarred.

Signed:

Harry W Hind

Harry W. Hind
President, Hind Health Care, Inc.

5-31-96

Date

DEPUTY DIRECTOR'S REVIEW

ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS DIVISION -- HFD-550

NDA #:	**20-619**
SUBMISSION DATE:	June 1, 1998.
TYPE:	Response to N/A letter.
REVIEW DATE:	December 2, 1998.
REVIEWER:	John Hyde, Ph.D., M.D.
NAME:	**Lidoderm Patch** (lidocaine patch 5%)
SPONSOR:	Hind Health Care
PHARMACOLOGIC CATEGORY:	Topical analgesic.
PROPOSED INDICATIONS:	Post-herpetic neuralgia.
DOSAGE FORM & ROUTE:	Patch, topical dermal
NDA DRUG CLASSIFICATION:	Analgesic
RELATED REVIEWS:	Medical Officer Review of 12/1/98 Statistical Review of 11/19/98 Med. Team Leader Review of 3/33/97 Medical Officer Review of 10/11/96 Statistical Review of 6/11/96
CSO:	V. Lutwak

BACKGROUND:

This NDA was originally submitted 5/31/96. The major clinical elements were a Phase 2 single-dose crossover study in post-herpetic neuralgia (PHN) and a two-center, multiple-dose, parallel study in PHN. Although the Medical Reviewer recommended approval, the Medical Team Leader felt that the submission did not present substantial evidence of efficacy, principally because there were no statistically significant differences in the primary endpoints of the multiple-dose study, although sporadic differences could be seen in other selected endpoints, notably allodynia. A non-approvable letter was issued 4/17/97 citing clinical and CMC deficiencies.

A meeting (EOP2-type) was held with the applicant on 7/21/97 and attended by the ODE V Officer Director. It was agreed that the application would be acceptable for refiling with <u>one</u> additional efficacy study. It was agreed that a withdrawal design would be acceptable. Such a study was conducted by the applicant, and a "complete response" amendment was submitted 6/1/98 with new clinical data and revised CMC information.

The clinical study was strongly positive, but the Medical Reviewer had some reservations about adequacy of the totality of the evidence for efficacy. (The CMC issues have been addressed adequately.)

DISCUSSION:

The statistical strength of evidence from the withdrawal study ($p < .001$) is at least as good as what might be obtained from two separate studies that could be considered substantial evidence with $p < .045$ (one-tail equivalent is $p=.0225$; probability for two such results is .0005063, which corresponds to a two-sided test with $p=.0010125$).

Evidence for efficacy can be considered to come from more than one study. The single-dose phase 2 crossover study, although by no means a replicate of the withdrawal study, provided some evidence of efficacy. The 3-week parallel study also provided some evidence of effect on allodynia, although the analysis was post-hoc and can only be considered supportive.

Topical lidocaine 0.5% to 4% is recognized as an effective topical analgesic for purposes of the external analgesic tentative final monograph. Either increasing the concentration to 5% or adding an occlusive dressing should be considered to provide at least as much efficacy (but would raise questions of safety). This provides some efficacy support, albeit not for the specific indication of PHN.

It is hard to quantify the benefit from this product. However, because of the relative systemic safety of the dosage form and the topical safety demonstrated in clinical testing, even a fairly modest benefit would still produce an acceptable risk/benefit ratio.

The total clinical package is less than ideal, and its adequacy might well be questioned if this were a new systemic therapy. However, taking all factors into account, and considering the data in aggregate, it appears that there is minimally adequate evidence for the efficacy of this product, so that the agency can abide by its EOP2 commitment to accept the one additional study.